STN - Structure Search 5-10-05

10/755,136

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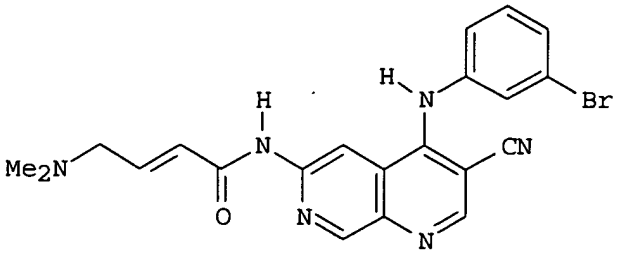
L9 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:189148 CAPLUS
DOCUMENT NUMBER: 140:406725
TITLE: Syntheses and EGFR kinase inhibitory activity of 6-substituted-4-anilino [1,7] and [1,8] naphthyridine-3-carbonitriles
AUTHOR(S): Wissner, Allan; Hamann, Philip R.; Nilakantan, Ramaswamy; Greenberger, Lee M.; Ye, Fei; Rapuano, Timothy A.; Loganzo, Frank
CORPORATE SOURCE: Chemical and Screening Sciences and Oncology Research, Wyeth Research, Pearl River, NY, 10965, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(6), 1411-1416
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



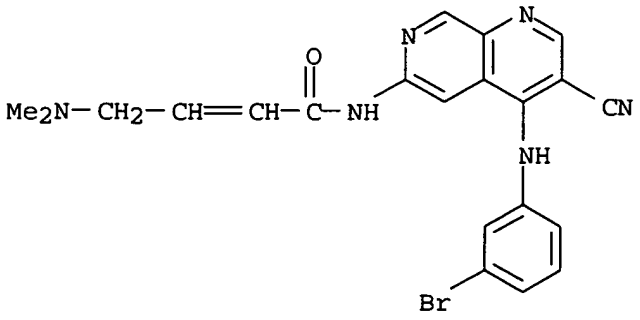
I

AB The syntheses and EGFR kinase inhibitory activity of a series of 6-substituted-4-anilino [1,7] and [1,8] naphthyridine-3-carbonitriles, e.g. I, are described. Both reversible and irreversible binding inhibitors were prepared These series were compared with each other and with the corresponding 4-anilinoquinoline-3-carbonitriles. Compds. having a 1,7-naphthyridine core structure can retain high potency while those with a 1,8-naphthyridine core are significantly less active. These results are consistent with mol. modeling observations.

IT **305371-24-8P 305371-37-3P 305371-40-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and EGFR kinase inhibitory activity of anilinonaphthyridinecarbonitriles)

RN 305371-24-8 CAPLUS

CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



RN 305371-37-3 CAPLUS
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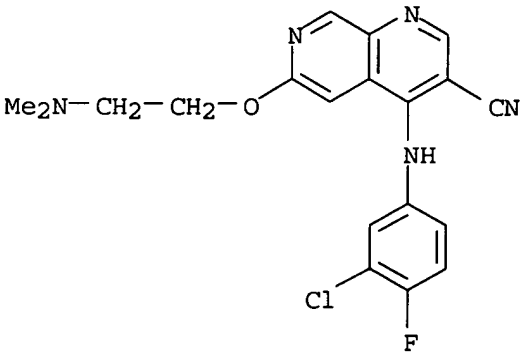
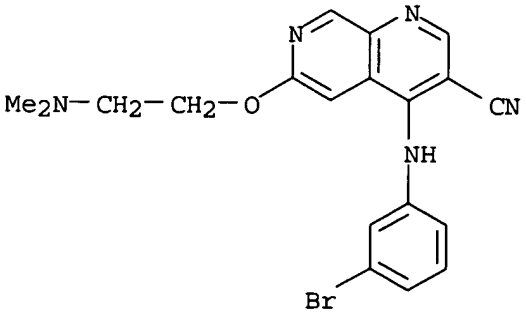
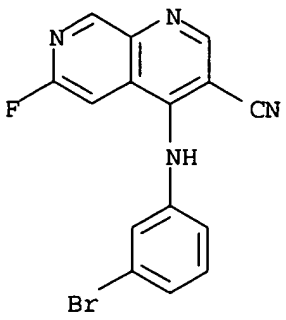


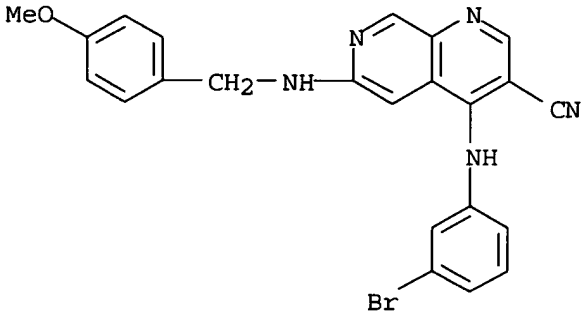
RN 305371-40-8 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-[2-(dimethylamino)ethoxy]- (9CI) (CA INDEX NAME)



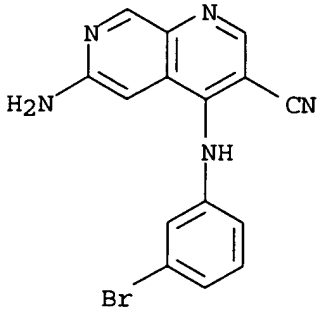
IT **305371-19-1P 305371-20-4P 305371-21-5P 305371-33-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and EGFR kinase inhibitory activity of anilinonaphthyridinecarbonitriles)
RN 305371-19-1 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-fluoro- (9CI) (CA INDEX NAME)



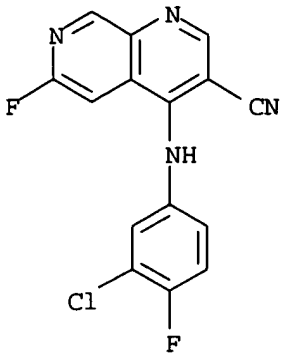
RN 305371-20-4 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-[[(4-methoxyphenyl)methyl]amino]- (9CI) (CA INDEX NAME)



RN 305371-21-5 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 6-amino-4-[(3-bromophenyl)amino]- (9CI) (CA INDEX NAME)



RN 305371-33-9 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-chloro-4-fluorophenyl)amino]-6-fluoro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:790501 CAPLUS
DOCUMENT NUMBER: 133:350203
TITLE: Substituted 3-cyano-[1.7]-, -[1.5]-, and -[1.8]-naphthyridine inhibitors of tyrosine kinases
INVENTOR(S): Wissner, Allan; Hamann, Philip Ross; Yamashita, Ayako
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066583	A1	20001109	WO 2000-US10250	20000418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2365212	AA	20001109	CA 2000-2365212	20000418
BR 2000009870	A	20020108	BR 2000-9870	20000418
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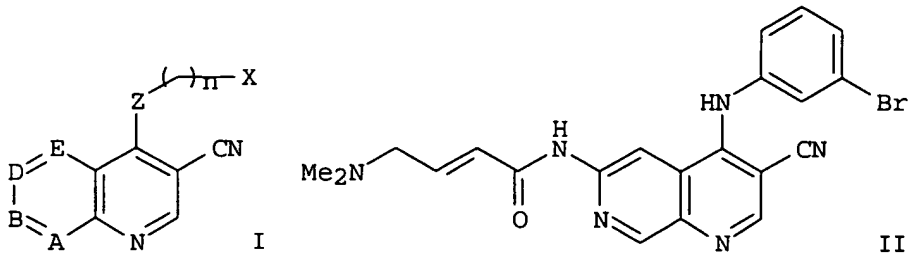
PT 1171440	T	20040730	PT 2000-926043	20000418
AU 776962	B2	20040930	AU 2000-44639	20000418
ES 2216884	T3	20041101	ES 2000-926043	20000418
ZA 2001008015	A	20030102	ZA 2001-8015	20010928
NO 2001005062	A	20011018	NO 2001-5062	20011018
US 2002165229	A1	20021107	US 2001-32587	20011221
US 6548496	B2	20030415		
HK 1040077	A1	20040910	HK 2002-101412	20020225

PRIORITY APPLN. INFO.: US 1999-155255P P 19990421
US 1999-295507 A 19990421
US 2000-550824 A3 20000418
WO 2000-US10250 W 20000418

OTHER SOURCE(S): MARPAT 133:350203

GI



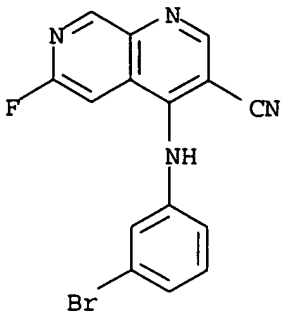
I II

AB This invention provides title compds. I [X = certain (un)substituted cycloalkyl, pyridinyl, pyrimidinyl, Ph, bicyclic aryl, or bicyclic heteroaryl; Z = NH, O, S, or NR; R = alkyl or carboalkyl; A:BD:E = (un)substituted CH:CHCH:N, CH:NCH:CH, N:CHCH:CH; n = 0-1; with numerous provisos] and their pharmaceutically acceptable salts. The compds. are inhibitors of protein tyrosine kinase, useful for treating certain cancers, polycystic kidney disease, colonic polyps, etc. A variety of example compds. and intermediates were prepared in 86 examples. For instance, 4-bromobut-2-enoyl chloride (prepared from TMS ester) was amidated with 6-amino-4-(3-bromophenylamino)-1,7-naphthyridine-3-carbonitrile, and the resultant halo amide (1:1 mixture of chloro and bromo compds.) was rebrominated with NaBr and aminated with Me2NH to give title compound II. The latter compound inhibited growth of a variety of human tumor cell lines in vitro, e.g., SKBR3 with an IC50 of 0.03565 μM/mL. Inhibitions of various receptor tyrosine kinases by I were determined for selected compds.

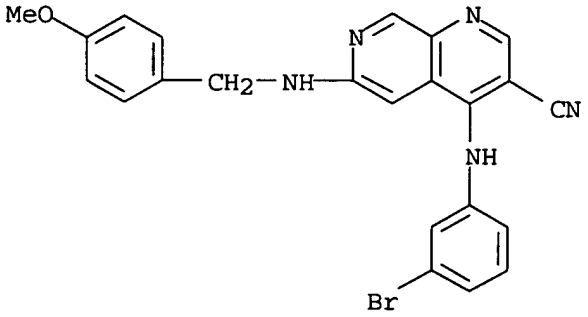
IT **305371-19-1P**, 4-(3-Bromophenylamino)-6-fluoro-1,7-naphthyridine-3-carbonitrile **305371-20-4P**, 4-(3-Bromophenylamino)-6-(4-methoxybenzylamino)-1,7-naphthyridine-3-carbonitrile **305371-21-5P**, 6-Amino-4-(3-bromophenylamino)-1,7-naphthyridine-3-carbonitrile **305371-30-6P**, 6-Fluoro-4-(3-hydroxy-4-methylphenylamino)-1,7-naphthyridine-3-carbonitrile **305371-31-7P**, 6-Fluoro-4-(4-phenoxyphenylamino)-1,7-naphthyridine-3-carbonitrile **305371-32-8P**, 4-(2,4-Dichlorophenylamino)-6-fluoro-1,7-naphthyridine-3-carbonitrile **305371-33-9P**, 4-(3-Chloro-4-fluorophenylamino)-6-fluoro-1,7-naphthyridine-3-carbonitrile **305371-34-0P**, 4-(4-Chloro-2-fluorophenylamino)-6-fluoro-1,7-naphthyridine-3-carbonitrile **305371-47-5P**, 4-(3-Bromophenylamino)-6-(trimethylsilanylethynyl)-1,7-naphthyridine-3-carbonitrile
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of substituted cyanonaphthyridine inhibitors of tyrosine kinases)

RN 305371-19-1 CAPLUS

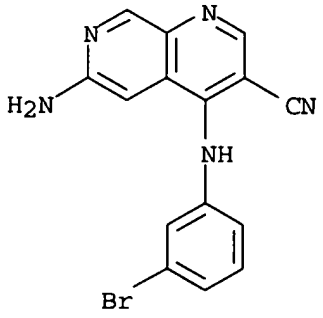
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-fluoro- (9CI) (CA INDEX NAME)



RN 305371-20-4 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-[[(4-methoxyphenyl)methyl]amino]- (9CI) (CA INDEX NAME)



RN 305371-21-5 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 6-amino-4-[(3-bromophenyl)amino]- (9CI) (CA INDEX NAME)



RN 305371-30-6 CAPLUS
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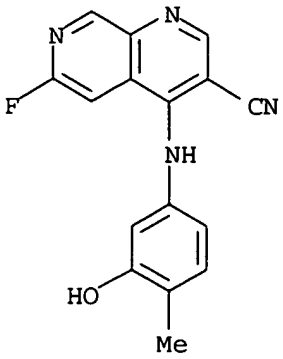

RN 305371-31-7 CAPLUS
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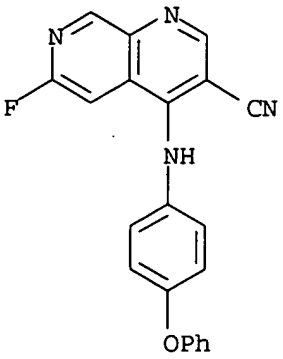
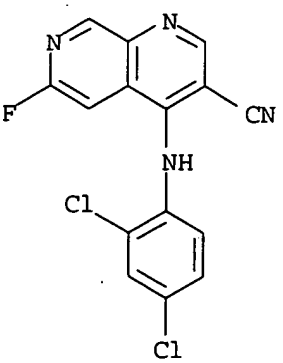
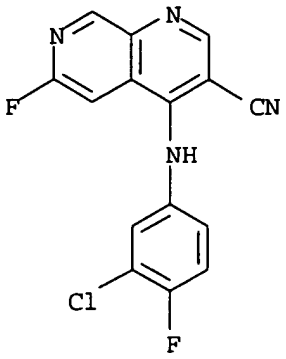
(9CI) (CA INDEX NAME)



RN 305371-32-8 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(2,4-dichlorophenyl)amino]-6-fluoro-
(9CI) (CA INDEX NAME)



RN 305371-33-9 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-chloro-4-fluorophenyl)amino]-6-
fluoro- (9CI) (CA INDEX NAME)



RN 305371-34-0 CAPLUS
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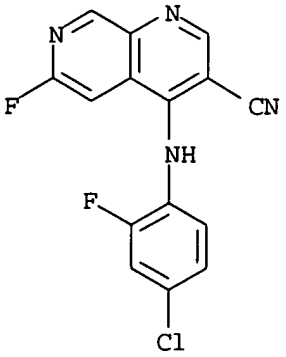
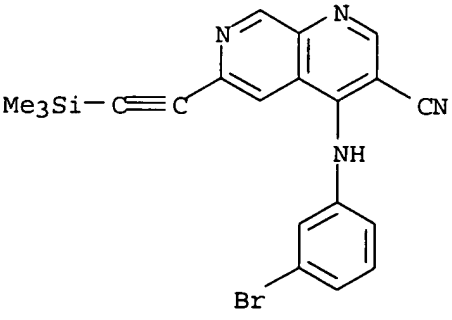


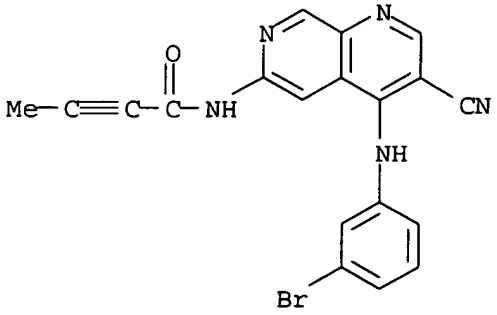
RN 305371-47-5 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-[(trimethylsilyl)ethynyl]- (9CI) (CA INDEX NAME)



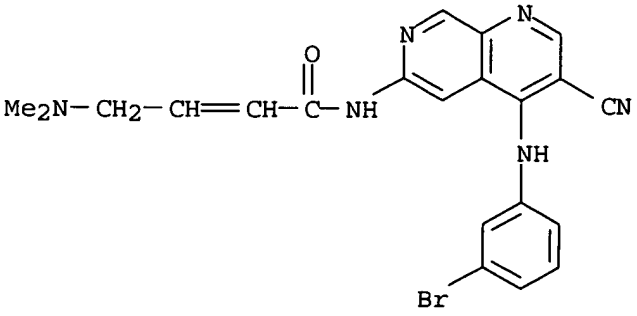
IT **305371-23-7P**, But-2-ynoic acid [4-(3-bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]amide **305371-24-8P**, 4-Dimethylaminobut-2-enoic acid [4-(3-bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]amide **305371-27-1P**, 4-(3-Bromophenylamino)-6-(2-morpholin-4-ylethylamino)1,7-naphthyridine-3-carbonitrile **305371-28-2P**, 4-(3-Bromophenylamino)-6-methylamino-1,7-naphthyridine-3-carbonitrile **305371-29-3P**, 1-[4-(3-Bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]-4-dimethylaminopyridinium fluoride **305371-35-1P**, 4-(4-Chloro-2-fluorophenoxy)-6-fluoro-1,7-naphthyridine-3-carbonitrile **305371-36-2P**, 6-(2-Dimethylaminoethoxy)-4-(4-phenoxyphenylamino)-

1,7-naphthyridine-3-carbonitrile **305371-37-3P**, 4-(3-Chloro-4-fluorophenylamino)-6-(2-dimethylaminoethoxy)-1,7-naphthyridine-3-carbonitrile **305371-38-4P**, 4-(2,4-Dichlorophenylamino)-6-(2-dimethylaminoethoxy)-1,7-naphthyridine-3-carbonitrile **305371-39-5P**, 4-(4-Chloro-2-fluorophenylamino)-6-(2-dimethylaminoethoxy)-1,7-naphthyridine-3-carbonitrile **305371-40-8P**, 4-(3-Bromophenylamino)-6-(2-dimethylaminoethoxy)-1,7-naphthyridine-3-carbonitrile **305371-41-9P**, 6-(2-Dimethylaminoethoxy)-4-(3-hydroxy-4-methylphenylamino)-1,7-naphthyridine-3-carbonitrile **305371-44-2P**, 4-(3-Bromophenylamino)-6-chloro-1,7-naphthyridine-3-carbonitrile **305371-49-7P**, 4-(3-Bromophenylamino)-6-ethynyl-1,7-naphthyridine-3-carbonitrile **305371-50-0P**, 1-[4-(3-Bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]-4-dimethylaminopyridinium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of substituted cyanonaphthyridine inhibitors of tyrosine kinases)

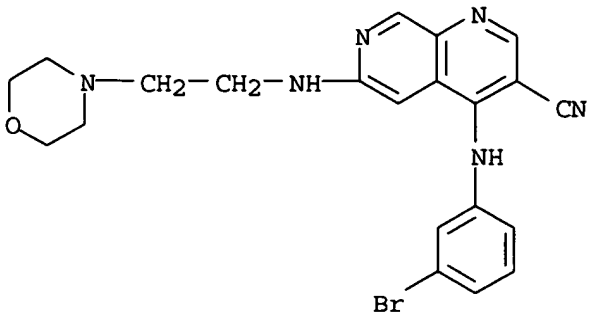
RN 305371-23-7 CAPLUS
CN 2-Butynamide, N-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]- (9CI) (CA INDEX NAME)



RN 305371-24-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



RN 305371-27-1 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-[[2-(4-morpholinyl)ethyl]amino]- (9CI) (CA INDEX NAME)



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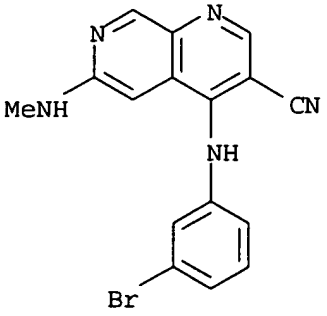
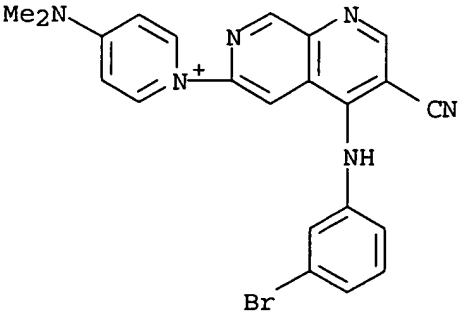
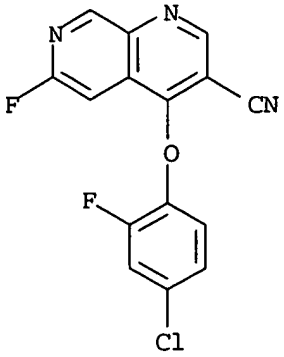


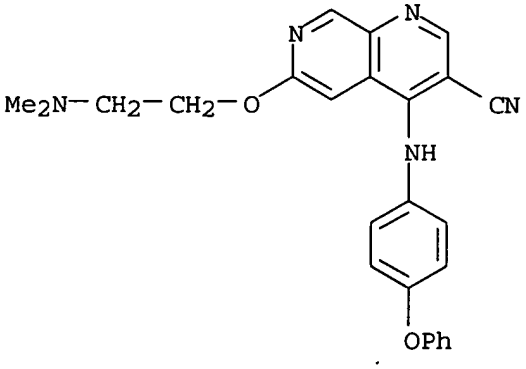
RN 305371-29-3 CAPLUS
CN Pyridinium, 1-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]-4-
(dimethylamino)-, fluoride (9CI) (CA INDEX NAME)



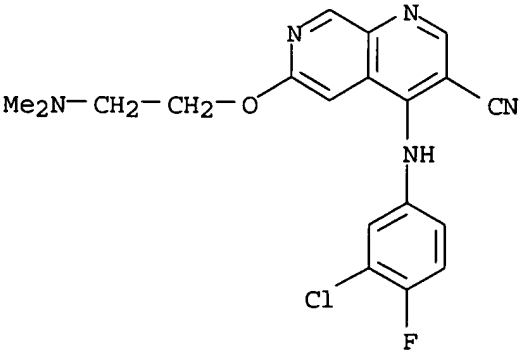
RN 305371-35-1 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-(4-chloro-2-fluorophenoxy)-6-fluoro-
(9CI) (CA INDEX NAME)



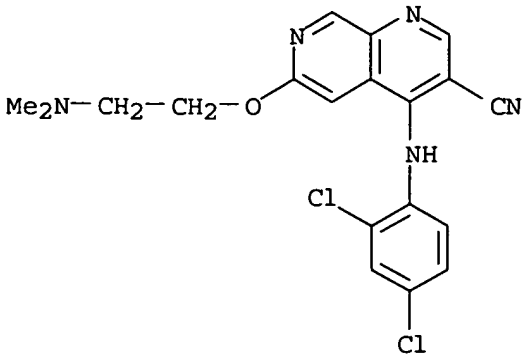
RN 305371-36-2 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 6-[2-(dimethylamino)ethoxy]-4-[(4-phenoxyphenyl)amino]- (9CI) (CA INDEX NAME)



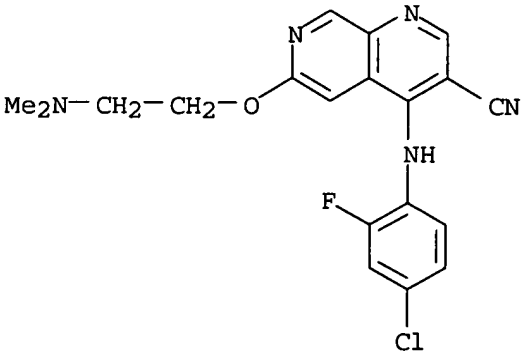
RN 305371-37-3 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-(dimethylamino)ethoxy]- (9CI) (CA INDEX NAME)



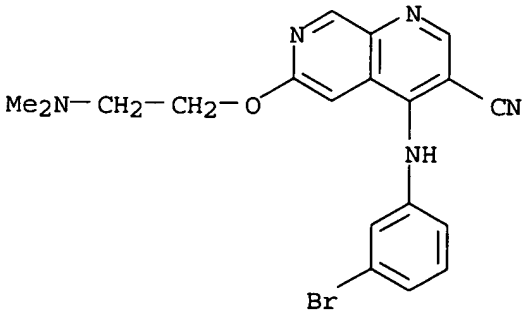
RN 305371-38-4 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(2,4-dichlorophenyl)amino]-6-[2-(dimethylamino)ethoxy]- (9CI) (CA INDEX NAME)



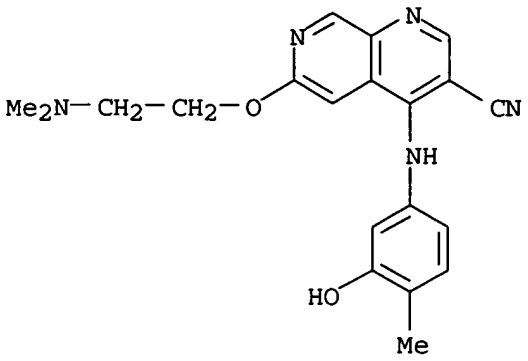
RN 305371-39-5 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(4-chloro-2-fluorophenyl)amino]-6-[2-(dimethylamino)ethoxy]- (9CI) (CA INDEX NAME)



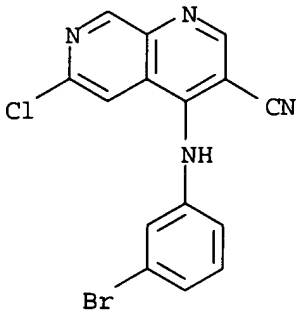
RN 305371-40-8 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-[2-(dimethylamino)ethoxy]- (9CI) (CA INDEX NAME)



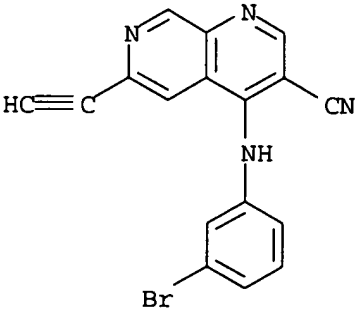
RN 305371-41-9 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 6-[2-(dimethylamino)ethoxy]-4-[(3-hydroxy-4-methylphenyl)amino]- (9CI) (CA INDEX NAME)



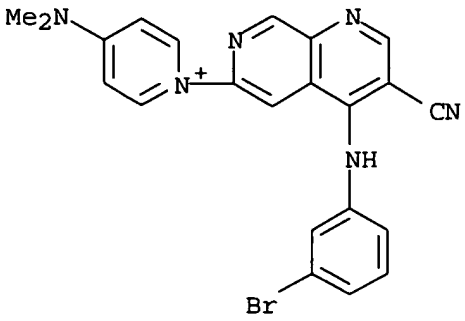
RN 305371-44-2 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-chloro- (9CI) (CA INDEX NAME)



RN 305371-49-7 CAPLUS
CN 1,7-Naphthyridine-3-carbonitrile, 4-[(3-bromophenyl)amino]-6-ethynyl- (9CI) (CA INDEX NAME)



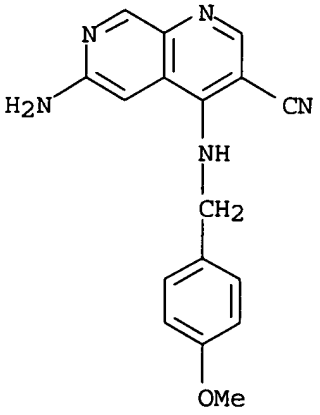
RN 305371-50-0 CAPLUS
CN Pyridinium, 1-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



IT **305371-22-6P**, 6-Amino-4-(4-methoxybenzylamino)-1,7-naphthyridine-3-carbonitrile **305371-25-9P**, 4-Bromobut-2-enoic acid [4-(3-bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]amide **305371-26-0P**, 4-Chlorobut-2-enoic acid [4-(3-bromophenylamino)-3-cyano-1,7-naphthyridin-6-yl]amide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of substituted cyanonaphthyridine inhibitors of tyrosine kinases)

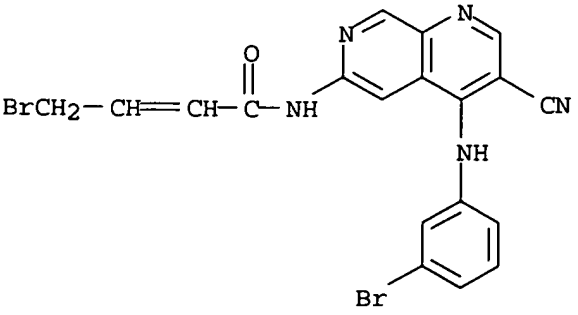
RN 305371-22-6 CAPLUS

CN 1,7-Naphthyridine-3-carbonitrile, 6-amino-4-[[(4-methoxyphenyl)methyl]amino]- (9CI) (CA INDEX NAME)

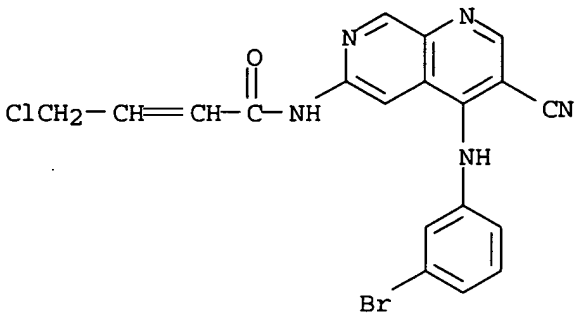


RN 305371-25-9 CAPLUS

CN 2-Butenamide, 4-bromo-N-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]- (9CI) (CA INDEX NAME)



RN 305371-26-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-3-cyano-1,7-naphthyridin-6-yl]-4-chloro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 09:30:44 ON 10 MAY 2005)

FILE 'REGISTRY' ENTERED AT 09:30:54 ON 10 MAY 2005
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 0 S L1 FULL
L4 STRUCTURE UPLOADED
L5 0 S L4
L6 STRUCTURE UPLOADED
L7 3 S L6
L8 27 S L6 FULL

FILE 'CAPLUS' ENTERED AT 09:35:30 ON 10 MAY 2005
L9 2 S L8

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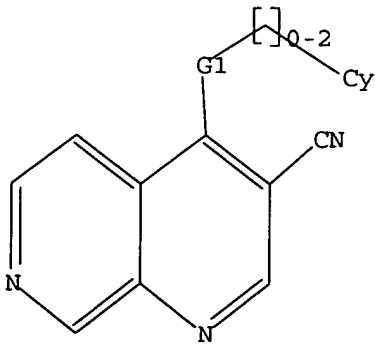
L6 HAS NO ANSWERS
L6 STR



G1 O,S,N
G2 Cy,Ak

Structure attributes must be viewed using STN Express query preparation.

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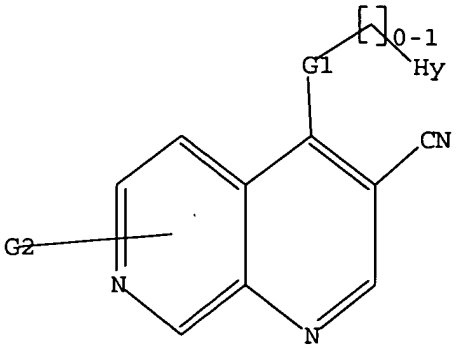
L1 HAS NO ANSWERS
L1 STR



G1 O,S,N
G2 Cy,Ak

Structure attributes must be viewed using STN Express query preparation.

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